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Review article

The definition and diagnostic testing of physical and cholinergic urticarias – EAACI/GA^{2}LEN/EDF/UNEV consensus panel recommendations

The recommendations for the definition and diagnosis presented in this position paper are the result of a panel consensus meeting held in December 2008 in Berlin. This consensus meeting was a joint initiative of EAACI (European Academy of Allergology and Clinical Immunology) Dermatology Section, the EU-funded network of excellence, GA^{2}LEN (Global Allergy and Asthma European Network), the EDF (European Dermatology Forum) and UNEV (urticaria network e.V.). The aim of these recommendations is to improve the diagnosis and management of patients with physical urticaria or cholinergic urticaria and to promote research and a better understanding of these diseases. Our recommendations used the paper produced by a 1996 expert meeting (1) and they acknowledge the latest changes in our understanding of physical urticarias and cholinergic urticaria as well as the recent development of novel diagnostic tools. In addition, this consensus paper highlights areas of need for further research.

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Physical and cholinergic urticarias

Physical urticaria is a heterogeneous group of inducible conditions that includes cold contact urticaria, symptomatic dermographism/urticaria factitia, heat contact urticaria, delayed pressure urticaria, and vibratory urticaria/angioedema. Physical urticarias are induced by exogenous physical triggers acting on the skin, including thermal (cold, heat), electromagnetic radiation (solar radiation) and mechanic triggers (friction, pressure, vibration). Physical urticarias need to be accurately distinguished from spontaneous urticaria as well as other inducible forms of urticaria (Table 1).

Cholinergic urticaria, which is also an inducible form of urticaria, is not classified as a physical urticaria (Table 1), because its symptoms are induced by an increase in the body core temperature and not by an exogenous physical trigger acting on the skin (2). The panel acknowledges that atypical and rare variants of cholinergic urticaria and of the physical urticarias not discussed below exist, but the discussion of these forms is beyond the scope of this article.

Physical urticarias and cholinergic urticaria are diagnosed on the basis of an indicative medical history and positive provocation testing. All patients with a history suggestive of a physical urticaria or cholinergic urticaria

Table 1. Classification of urticaria

Group	Subgroup	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous weal and/or angioedema <6 weeks
	Chronic spontaneous urticaria	Spontaneous weal and/or angioedema ≥6 weeks
Physical urticarias	Cold contact urticaria	Eliciting factor: skin contact with cold air/water/solids
	Delayed pressure urticaria*	Eliciting factor: vertical sustained pressure
	Heat contact urticaria	Eliciting factor: skin contact with hot air/water/solids
	Solar urticaria	Eliciting factor: UV and/or visible light
	Symptomatic* dermographism/Urticaria factitia	Eliciting factor: mechanical stroking
	Vibratory urticaria/angioedema	Eliciting factor: vibration (e.g. pneumatic hammer)
Other inducible urticarias	Aquagenic urticaria	Eliciting factor: water contact at any temperature
	Contact urticaria	Eliciting factor: contact with an allergic or nonallergic stimulus
	Cholinergic urticaria	Eliciting factors: increase of body core temperature
	Exercise induced urticaria/anaphylaxis	Eliciting factor: physical exercise

*Urticaria of all types can present with an immediate weal and flare and/or angioedema, except for delayed pressure urticaria which is characterized by deep swellings arising with a 1/2 – 12 h latency and symptomatic dermographism, which does not present with angioedema.

should be offered provocation testing if possible. Care must be taken for all provocation tests as patients with a severe physical or cholinergic urticaria may develop systemic symptoms including shock. Consequently, facilities for emergency treatment should be available.

Patients may present with more than one physical urticaria (3, 5). Therefore, all patients with physical urticaria should be tested for all physical triggers that appear to be relevant from the medical history. Physical urticarias and cholinergic urticaria are commonly present in patients who concomitantly exhibit chronic spontaneous urticaria and also occur with other chronic inducible urticarias.

General recommendations for provocation testing

The results of provocation tests may be influenced by the patients' treatment, which should therefore be withdrawn prior to testing. The response in patients who are unable to stop treatment should be evaluated with caution. Retesting during therapy may be useful to assess the response to it. Testing should be performed in skin sites which have not been recently affected by urticaria because skin sites exhibit a refractory period after urticarial reactions. Patients with cholinergic urticaria should be asymptomatic for at least 48 h before provocation testing if possible. Provocation testing using physical triggers should be performed at the recommended skin sites (see below and Fig. 1). If the test is negative despite a strong suspicion of a physical urticaria from the medical history, the test may be repeated at a skin site which, according to the patient, has been affected previously. In some cases, physical urticarias cannot be confirmed by standard provocation testing, at the time of testing.

The onset of positive test responses is usually rapid, i.e. within minutes. An exception to this rule is delayed pressure urticaria, where it is often necessary to depend on the patient to report delayed provocation test responses if they occur. Physical urticarias and cholinergic urticaria may have important occupational and employment implications.

Physical urticarias and cholinergic urticaria can present with weals and/or angioedema (except symptomatic dermographism: no angioedema and delayed pressure urticaria: no weals) and systemic reactions can occur (6). Patients exhibit individual trigger thresholds which may vary with time and treatment (7). Threshold testing in most cases allows, for an estimation of the activity of the disease at that time point.

Symptomatic dermographism

Symptomatic dermographism (Syn. urticaria factitia, dermographic urticaria) is the most common subtype of physical urticaria (Table 1). Symptomatic dermographism should be differentiated from simple dermographism where wealing, but not pruritus, occurs after moderate stroking of the skin (3). Symptomatic dermographism is characterized by the development of itching and wealing at a lower force than that required to induce simple dermographism (8). Other types of dermographism such as white dermographism (in atopic patients) are unrelated to symptomatic dermographism.

Provocation testing should be performed by stroking the skin lightly with a smooth blunt object (e.g. the tip of a closed ball point pen or a wooden spatula) or a purpose-built instrument, known as a dermographometer, where one is available. A dermographometer is

Patient information

Name:

Date of birth:

Instructions:

Perform testing as indicated and document presence (+) or absence (-) of weal (W), erythema (E), pruritus (P) and/or angioedema (A) as well as date / time of testing and who performed the test.

1. Symptomatic Dermographism (Urticaria factitia)

Testsite: Upper back / Volar forearm
Test: Moderate stroking of the skin with a blunt smooth object (e. g. closed ballpoint pen tip, wooden spatula) /dermographometer (36 g/mm^2)
Reading time: 10 minutes after testing

W	P

Date / Time _____ Test done by _____

If weal and pruritus: Test threshold with dermographometer →

2. Cold contact urticaria

Testsite: Volar forearm / abdomen
Test: Melting ice cube in thin plastic bag/Temp*Test (*4°C) for 5 minutes
Reading times: 10 minutes after testing

W	P

Date / Time _____ Test done by _____

If weal: Test cold stimulation time or temperature threshold →

3. Heat contact urticaria

Testsite: Volar forearm
Test: Heat source/Temp*Test (*45°C) for 5 minutes
Reading times: 10 minutes after testing

W	P

Date / Time _____ Test done by _____

If weal: Test cold stimulation time or temperature threshold →

4. Delayed pressure urticaria

Testsite: Shoulder/Upper Back/Thighs/Volar forearm
Test: Suspension of weights over shoulder (7 kg, shoulder strap width: 3 cm) for 15 min or weighted rods (1.5 cm diameter: 2.5 kg; or 6.5 cm diameter: 5 kg) for 15 min. Dermographometer at 100 g/mm^2 for 70 sec
Reading times: ≈6 hours after testing

A	E

Date / Time _____ Test done by _____

If angioedema: Test threshold →

5. Solar urticaria

Testsite: Buttocks
Test: UVA 6 J/cm^2 & UVB 60 mJ/cm^{2}irradition (e. g. Saalmann Multitester SBC LT 400) Visible light (projector)
Reading times: 10 minutes after testing

	W	P
UVA		
UVB		
Visible light		

Date / Time _____ Test done by _____

If weal: Test threshold →

6. Vibratory urticaria/angioedema

Testsite: Volar forearm
Test: Vortex vibrator for 10 minutes, 1000 rpm
Reading times: 10 minutes after testing

A	P

Date / Time _____ Test done by _____

7. Cholinergic Urticaria

Test 1: Exercise using a machine, e. g. bicycle trainer or treadmill, to the point of sweating, then continue for 15 minutes,

if positive test reaction:

Test 2: 42 ºC bath, monitor body temperature. Continue bath for 15 min after body temperature has increased by ≥ 1°C over baseline

Reading times: Immediately and 10 minutes after end of test

1. Exercise	W	P

If positive reaction →

2. Hot bath	W	P

Figure 1. Provocation testing for physical and cholinergic urticaria.

Threshold testings

1. Symptomatic dermographism (Urticaria factitia)

Testsite: Upper back
Test: Moderate stroking of the skin with a dermographometer
Reading time: 10 minutes after testing

g/mm²	20	36	60
P			
W			

Date / Time _____

Test done by _____

2. Cold contact urticaria

Testsite: Volar forearm
Test: Temp*Test*®/water bath for 5 minutes, or melting ice cube
Reading times: 10 minutes after end of testing

Ice cube, stimulation time threshold testing

	30 sec	1 min	2 min	5 min
P				
W				

Date / Time _____

Test done by _____

TempTest®, temperature threshold testing

°C:	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
P																
W																

°C:	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
P																
W																

3. Heat contact urticaria

Testsite: Volar forearm
Test: Heat source/Temp*Test*®, 5 minutes
Reading times: 10 minutes after testing

°C:	45	44	43	42	41	40	39	38	37	36
P										
W										

Date / Time _____

Test done by _____

4. Delayed pressure urticaria

Testsite: Volar forearm (rod), upper back (dermographometer)
Test Weighted rods (6.5 cm diameter) for 15 min or Dermographometer at 100g/mm²
Reading times: ≈6 hours after testing

Weighted rod

kg:	1	2	3	4	5
A					
E					

Date / Time _____

Test done by _____

Dermographometer 100g/mm²

sec:	20	30	40	50	60
A					
E					

5. Solar urticaria

Testsite: Buttocks
Test: UVA & UVB irradiation (e. g. Saalmann Multitester SBC LT 400)
Reading times: 10 minutes after testing

UVA J/cm²	P	W
2,4		
3,3		
4,2		

UVB mJ/cm²	P	W
24		
33		
42		

Date / Time _____

Test done by _____

Figure 1. (Continued)

designed to apply a rubbing stimulus to a subject's skin using predefined and reproducible pressures. A calibrated dermographometer is commercially available (HTZ Limited, Vulcan Way, New Addington, Croydon, Surrey, UK). It has a spring-loaded smooth steel tip 0.9 mm in diameter. The pressure on the tip can be varied by turning a screw at the top of the instrument. The scale settings from 0 to 15 are equivalent to a range of tip pressures from 20 to 160 g/mm^2.

For the diagnosis of symptomatic dermographism, the smooth blunt object should be held perpendicular to and used to apply a light stroking pressure to the skin of the upper back or volar forearm (Fig. 1). The skin at the test site should be unbroken and free of obvious signs of infection. If a dermographometer is available, three parallel lines (up to 10 cm long) should be made with dermographometer settings equivalent to 20, 36 and 60 g/mm^2.

The reaction is considered positive in patients off antihistamines who show a weal response 'and' report pruritus at the site of provocation at 36 g/mm^2 (353 kPa) or less. A weal response without itch on provocation at 60 g/mm^2 (589 kPa) or higher indicates simple dermographism. The test response should be read 10 min after testing (9).

Cold contact urticaria

Cold contact urticaria (Syn. acquired cold urticaria) is defined by the appearance of wealing responses after contact cooling of the skin (Table 1) (10, 11). Provocation testing should be performed by applying a cold stimulus to the skin of the volar forearm. Cold provocation methods include the traditional ice cube test, testing with cool packs or cold water baths, and Temp*Test*® measurements (Fig. 1). If an ice cube is used for testing, it should be melting to avoid cold damage of the skin and contained within a thin plastic bag to prevent direct water contact to avoid any confusion with aquagenic urticaria if the test is positive (12). The use of cool packs and cold water baths requires special care, because these methods carry a small risk of inducing systemic reactions. Temp*Test*® is a Peltier element-based provocation device. It is currently approved for research purposes but would need approval as a medical device before it could be used routinely in specialist urticaria clinics. The Temp*Test* 3.0 model (emo systems GmbH, Berlin, Germany) can test for 12 different temperatures simultaneously (between 4°C and 40 ± 0.1°C). The use of Temp*Test*® allows for reproducible and standardized cold provocation tests and the identification of temperature and stimulation time thresholds (13).

Ice cube testing should be performed for 5 min. In some patients shorter or longer provocation times may be appropriate, e.g. 30 s (in patients that are very sensitive and/or afraid of massive reactions) or up to 20 min in patients with a positive history but no weal after standard testing (14). Alternative test methods may be required in patients with a negative ice cube test, e.g. an arm can be immersed in cold water at 5–10°C for 10 min. Test sites should be inspected and test responses should be assessed 10 min after the end of provocation testing.

The test should be considered positive if the test site shows a palpable and clearly visible weal and flare type skin reaction. This reaction will in most cases be itchy and/or associated with a burning sensation. In patients that show a positive test reaction, threshold testing should be performed if possible. The knowledge of their threshold may help patients to avoid risky situations and their physician to optimize treatment. Threshold testing can determine the stimulation time threshold (15), which is the shortest duration of cold exposure required to induce a positive test reaction. Stimulation time thresholds are determined by varying the time of cold application needed to induce a weal and flare type skin response (Fig. 1). Temperature thresholds, i.e. the highest temperature sufficient to induce a positive test reaction, can be assessed with Temp*Test*®, but not by ice cube testing. Temperature thresholds should be determined whenever Temp*Test*® is available, as this information can help patients to avoid risky situations in their daily lives.

Heat contact urticaria

Heat contact urticaria is a rare physical urticaria defined by the appearance of wealing responses after contact heating of the skin within minutes after exposure (Table 1) (16).

Provocation testing should be performed by applying a hot stimulus to the skin of the volar forearm. Heat provocation methods that can be used for skin testing include testing with metal/glass cylinders filled with hot water, hot water baths, or Temp*Test*® measurements (Fig. 1).

Heat should be applied for 5 min at a temperature of 45°C. In some patients shorter or longer provocation times and higher temperatures may be appropriate. Test sites should be inspected and test responses should be assessed 10 min after provocation testing. The test should be considered positive if the test site shows a palpable and clearly visible weal and flare type skin reaction. This reaction will in most cases be itchy and/or associated with a burning sensation.

In patients that show a positive test reaction, stimulation time and temperature thresholds should be determined. Thresholds may allow for the determination of disease activity and for assessing response to therapy. Heat contact urticaria must be differentiated from cholinergic urticaria and from solar urticaria.

Delayed pressure urticaria

Delayed pressure urticaria is defined by the appearance of a skin swelling response after the application of a

sustained pressure stimulus to the skin (Table 1) (17, 18). It may occur with other forms of urticaria, including spontaneous disease. Responses occur between 30 min and 12 h (usually 6–8 h) after exposure and may last up to 72 h. The principle of testing is the application of sustained pressure to the skin. Test methods include suspension of weights over the shoulder (7 kg on a 3 cm shoulder strap), the application of rods supported in a frame on the back, on thighs or forearm and the use of a dermographometer. The latter two methods allow for reproducible measurements and the assessment of thresholds.

In the first, weighted metal rods are lowered vertically onto the skin (forearm, back or anterior thighs). In the literature, the use of many different rod diameters and weights (with a wide range of pressures applied to the patient) is reported. Lawlor et al, e.g. used a rod of 1.5 cm diameter with weights of 2.29 kg (127 kPa) to 4.79 kg (266 kPa) for up to 15 min on the back (19). Barlow used rods that were 1.5 cm in diameter and weights of 2.5 kg (139 kPa) and 3.5 kg (194 kPa) resting on the anterior thighs for 20 min (20). The 5 kg rod used in the Charité Hospital on the patient's forearms for 15 min measures 6.5 cm in diameter (14.8 kPa). In case of testing with the dermographometer the device should be applied perpendicularly at 100 g/mm^2 (981 kPa) for 70 s on the upper back.

The test should be considered positive if the test site shows a delayed red palpable swelling. Test sites should be inspected and test responses should be assessed (by the patient or physician) approximately 6 h after the end of provocation testing. The reaction is not usually associated with pruritus but may be associated with a burning/painful sensation. Delayed pressure urticaria must be differentiated from symptomatic dermographism. Threshold testing should be performed in patients who show a positive test reaction. Threshold testing may allow the physician to assess disease activity and treatment responses.

Solar urticaria

Solar urticaria is defined by the appearance of a wealing response within minutes of exposure to sunlight (Table 1) (21, 22). Provocation testing should be performed by exposure to ultraviolet and visible radiation. Solar simulators with filters (UV-A and UV-B) or monochromator (UV-A and UV-B, visible light) should be used for provocation. Provocation should be done on the buttocks separately in the UV-A, UV-B and visible light range. UV-A should be tested at 6 J/cm^2 and UV-B at 60 mJ/cm^2. In patients with a negative reaction, visible light is tested by using a projector (e.g. slide projector, 10 cm distance). Positive provocation leads to a rapid urticarial response at the site of exposure within 10 min (Fig. 1). The test should be considered positive if the test site shows a palpable and clearly visible weal and flare type skin reaction. This reaction will in most cases be itchy and/or associated with a burning sensation. In patients that show a positive test reaction, threshold testing should be performed by varying the radiation dose, e.g. by changing the time of exposure to the standard light source. This threshold testing may allow for the determination of disease activity and response to therapy.

Vibratory urticaria/angioedema

Vibratory urticaria/angioedema is defined by the presence of itching and swelling within minutes at the site of skin exposure to vibration (Table 1) (23, 24). For diagnostic purposes, vibratory angioedema and weal can be reproduced using a laboratory vortex mixer. The forearm is held on a flat plate laid on the vortex mixer which is run between 780 rpm (22) or 1380 rpm (25) for 10 min. The site of application should be assessed for swelling 10 min after testing (Fig. 1). The measurement of the circumference of the arm before and after the challenge at 3 points (wrist, mid-forearm, elbow) can help define a vibration-induced swelling.

Cholinergic urticaria

Cholinergic urticaria is defined by itching and wealing after active heating up of the body core temperature (e.g. exercise) or passive heating (e.g. hot bath). A typical description is one of tiny short lived weals with a pronounced flare reaction that is frequently localized to the trunk and limbs (26, 27). Other morphological patterns, including angioedema, can occur. Cholinergic urticaria must be differentiated from exercise induced urticaria/anaphylaxis, which is induced by exercise but not passive warming and is more often associated with systemic symptoms than cholinergic urticaria. Food or drug-dependent exercise induced anaphylaxis should be considered in the differential diagnosis.

Provocation testing should be performed in a two step approach to differentiate cholinergic urticaria from exercise induced urticaria with certainty. Caution is advised in patients with pre-existing cardiac conditions. Pretesting examination should be done to record pre-existing skin lesions (e.g. acne papules) which may make assessment more difficult. The effects of therapy can be monitored by repeated testing. Moderate physical exercise appropriate to the patient's age and general condition should be undertaken (e.g. on a treadmill or stationary bicycle). Exercise should be performed to the point of sweating and up to 15 min beyond. Wearing warm clothing in a warm room facilitates the provocation tests. The test is positive if exercise challenge leads to the typical rash over 10 min. If the exercise provocation test is positive, a passive warming test should be done at least 24 h later (42°C full bath for up

to 15 min while recording body core temperature to achieve a rise of ≥1.0°C) to differentiate cholinergic urticaria from exercise induced anaphylaxis.

Areas in need of further research

The following questions require further research:

(1) identification of underlying causes and mast cell activating signals for inducible urticarias;
(2) epidemiology of inducible urticaria including subtypes;
(3) standardisation of diagnostic tools and test procedures in inducible urticarias;
(4) identification and characterization of the relevance of threshold determination for disease activity and monitoring of therapeutic effects; and
(5) optimization of disease management including the development and harmonization of protocols for desensitization.

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